REMARKS

As an initial matter, Applicant appreciates the courtesy extended by Examiner T. Truong during a telephonic interview conducted July 14, 2009. The provisional obviousness-type double patenting rejection of claims 11-13 and 23-25 and the §112, first paragraph rejection of claims 17-28 were discussed. No agreement was reached on the obviousness-type double patenting rejection. Applicants appreciate the indication that cancellation of the language "prevention or" from claims 17 and 23 would likely obviate the §112, first paragraph rejection.

Applicants appreciate the indication that claims 14-16 would be in a condition for allowance if rewritten as independent claims. Reconsideration of the above-identified application as amended is requested. Claims 11, 13-17, 19-23 and 25-28 are pending in the instant application. Claims 1-10, 12, 18, and 24 have been cancelled in this or a prior amendment without prejudice or disclaimer. Claims 11, 17 and 23 have been amended by the instant amendment. No new matter has been introduced by the instant amendments.

Claims 11-13 and 23-25 stand provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 25, 32 and 34 of copending application U.S.S.N. 10/480,559. The Office Action avers that "although the conflicting claims are not identical, they are not patentably distinct from each other because formula IV of the copending application embrace species of the instant claims 11-13.

Claim 12 and 24 have been cancelled by the instant amendment and claim 11 amended to cancel the species of claim 12. Thus, Applicants traverse the rejection in part and reserve the right to pursue the subject matter of claims 12 and 24 in a continuing application.

Although claims 11 (in part) and 13 of the instant application are directed to a species which is generically within the scope of claim 25 of the '559 application, Applicants present herewith a Declaration under 37 C.F.R. §132 of Dr. Leo Widler executed on October 13, 2009 which provides evidence that the compounds of instant claims 11 and 13 are non-obvious over the generic scope of claims 25 and 32 of the '559 application and non-obvious over the exemplified species recited in the specification of the '559 application.

More particularly, the §132 declaration of Dr. Widler presents pharmacokinetic and FLIPR inhibition data establishing that (1) the compound of claims 11 and 13 is more potent than the exemplified compounds of the '559 application and (2) the structural-activity relationship of the exemplified compounds in the '559 application would not lead a medicinal chemist of ordinary skill in the art to prepare the compound of claims 11 and 13.

As discussed in Dr. Widler's declaration, the compound of claim 13 exhibits a an averaged IC_{50} of 1.35 nM in the standard FLIPR assay, a C_{max} of 61.5 nM, a T_{max} of 1 hour, a bioavailability of 31% in rat and a W factor (C_{max}/IC_{50}) of 45 based on the in vitro and in vivo assays described in paragraphs 6 and 8 of the declaration. The combination of high potency, high C_{max} at an early time point (T_{max}) and short terminal half life exhibited by the compound of claim 13 are suitable to elicit a desirable bone anabolic effect, e.g., a desirable calcilytic effect.

In contrast, the most potent structurally related compound from the '559 application is Example 80 which has a 6-propargyloxy residue and an unsubstituted N(1)-benzyl residue on the quinazolin-2-one. Examples 90 and 120 incorporate para substituents on the N-benzyl residue of the compound of Example 80. The FLIPR potency of Example 80 is 4.4 nM and the potency of Examples 90 and 120 is 10 and 15 nM respectively. Thus, the '559 application would teach one of ordinary skill in the art that para substituted N-benzyl residues should have reduced potency. Earlier structure-activity relationship studies conducted on analogous quinazolin-2-one compounds having a 6-methoxy residue suggested that para substitution does not improve *in vitro* potency. Thus, Example 29, 6-methoxy-4-(4-isopropylphenyl)-N1-benzyl-quinazolin-2-one, exhibits substantially the same IC_{50} in the PI assay of paragraph 7 of Dr. Widler's declaration as the para-halogen substituted benzyl analogs of Examples 148-150 (Ex. 148 is the 4-chlorobenzyl, Ex. 149 is the 4-bromobenzyl and Ex. 150 is the 4-fluorobenzyl analog of Example 29). Other para-substituted benzyl analogs, e.g., Examples 152-154, are less potent than Examples 29 and 148-150.

For completeness, Dr. Widler's declaration further provides inhibitory data for the most potent compounds recited in the '559 application. As shown in Table 3, the most potent compounds of the '559 application have IC_{50} values of between 2 and 4 nM in the FLIPR assay, but carry a meta-substituted benzyl residue or a benzothiadiazolylmethyl residue on the N(1) of the quinazolin-2-one.

Dr. Widler's declaration further provides pharmacokinetic data for the compound of claim 13 and Examples 37 and 80 of the '559 application. As shown in Tables 1 and 4, the compound of claim 13 has a significantly improved "calcilytic"-like pharmacokinetic profile and shows better bioavailability compared to the aforementioned Examples.

One of ordinary skill in the art would not reasonably expect to obtain the combination of improved *in vitro* potency and desirable *in vivo* PK behavior exhibited by the compound of claim 13 based on the previously disclosed compounds from the '559 application. Thus, one of ordinary skill in the art, considering the breadth of claims 25 and 32 of the '559 application in combination with the structure-activity relationship trends set forth in Tables 2, 3 and 4 of Dr. Widler's declaration would not have motivation to prepare the specific compound recited in claim 13 of the instant application.

Thus, for at least the foregoing reasons, Applicants request withdrawal of the non-statutory obviousness-type double patenting rejection of claims 11 and 13.

Claim 23 is directed to pharmaceutical compositions comprising a compound of claim 11. Claim 25 is dependent from claim 23 and provides pharmaceutical compositions comprising the compound of claim 13 respectively. For at least the reasons that claims 11 and 13 are patentably distinct over claim 25 of the '559 application, claims 23 and 25 are patentably distinct over claim 32 of the '559 application.

Claim 34 of the '559 application was originally asserted as a basis for obviousness-type double patenting rejection of the generic claims 1, 2, and 8 is this application which provided compounds of Formula I or I'. Current claims 11 and 13 are directed to 4 species, each of which is patentably distinct from the species of claim 34 of the '559 application. Thus, the obvious-type double patenting rejection based on claim 34 should be withdrawn.

Claims 17-28 stand rejected under 35 U.S.C. §112, first paragraph, allegedly because the specification, while being enabling for the treatment of recited disorders, does not reasonably provide enablement for the prevention of said disorders, nor does it enable a composition of matter capable of preventing any disorders.

Claims 17-28, as amended, are directed to compositions and methods of treating recited disorders. Applicants reserve the right to pursue claims directed to methods of presenting disease using the compounds of the invention in one or more continuation applications.

Thus, claims 17-28, as presently amended, comply with the enablement requirement of §112, first paragraph.

In view of the above, it is respectfully submitted that all of the claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

Novartis Institutes for BioMedical Research, Inc.
220 Massachusetts Avenue
Cambridge, MA 02139

(617) 871-3105
Date: 13 October 2009

John Alexander
Attorney for Applicants
Reg. No. 48,399